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Intracranial Hemorrhage in Association With Thrombolytic Therapy: Incidence and Clinical Predictive Factors

PETER P. DE JAEGERE, MD, ALFRED A. ARNOLD, MD, AGGIE H. BALK, MD, MAARTEN L. SIMOONS, MD, FACC

Rotterdam, The Netherlands

In a period of 18 months, 2,469 patients with acute myocardial infarction treated with a thrombolytic agent were prospectively registered in 61 hospitals. Most patients (73%) were treated with streptokinase. Intracranial hemorrhage was observed in 24 patients, corresponding to an incidence rate of 1% (95% confidence interval 0.6% to 1.3%). The median time interval between the start of thrombolytic therapy and the first clinical signs of intracranial bleeding was 16 h (range 3 to 36). In total, 16 (66%) of the 24 patients died as a result of cerebral hematoma.

To determine clinical predictive factors, a case-control study was conducted. For every patient with intracranial hemorrhage, two control patients who received thrombolytic therapy because of acute infarction in the same hospital and in the same period were selected. Detailed clinical characteristics of 22 of the 24 patients as well as of 7 other patients with documented intracerebral bleeding from the European Cooperative Study Group and of 2 patients who sustained intracranial hemorrhage outside the registry period were compared with 62 control patients. The results of multivariate logistic regression analysis indicate that patients taking an oral anticoagulant before admission, patients with a body weight <70 kg and those >65 years old are at higher risk for intracranial hemorrhage during thrombolytic therapy.

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It has now been shown conclusively (1–13) that thrombolytic therapy reduces the mortality rate in patients with evolving myocardial infarction despite the increased risk of bleeding complications associated with this therapy. Overall, the severity and frequency of these hemorrhagic complications have been recognized to be acceptable and tolerable. Most bleeding complications are of minor importance and related to invasive vascular procedures. However, in a small number of patients, intracranial hemorrhage may occur. Reported incidence rates for intracranial hemorrhage in medium size and large trials (2,3,5,7,8,11,13,14) vary from 0% to 1.4%. The ability to recognize patients at increased risk for bleeding would help to further substantiate the indications and contraindications for this therapy. Therefore, this study was designed to define the incidence of intracranial hemorrhage in association with thrombolytic therapy in clinical practice and to identify clinical predictive factors.

Methods

Incidence. To determine the incidence of intracranial hemorrhage in association with thrombolytic therapy, all patients with an acute myocardial infarction treated with a thrombolytic agent were prospectively registered in 61 hospitals in The Netherlands. This registry was begun in October 1988 and was completed after 18 months. Every month, each participating center completed a special registry form in which the names of patients who received thrombolytic therapy were entered and in which those patients sustaining intracranial hemorrhage within the 1st 48 h after the start of thrombolytic therapy were identified. The recording of ischemic or unclassified cerebrovascular accidents was not required.

Clinical predictive factors. A case-control study was conducted to define clinical predictive factors for intracranial hemorrhage in association with thrombolytic therapy (15,16). For every patient with intracranial hemorrhage, two control patients who received thrombolytic therapy because of an evolving myocardial infarction in the same hospital in the same period were selected. The clinical characteristics of the patients with intracranial bleeding were compared with those of the control group, including age, low body weight (<70 kg), use of anticoagulant or antiplatelet drugs, or both, before admission, administration of heparin, oral anticoagulant or antiplatelet therapy alone or in combination after admission, hypertension on admission (systolic blood pressure >165 mm Hg diastolic blood pressure >95 mm Hg, or both, on at least two occasions before the start of therapy), history of hypertension (patient known to have hypertension and treated with at least one antihypertensive drug), peripheral vascular disease (history of intermittent claudication or vascular bruits on physical examination) and current smoking of cigarettes. In addition, demographic data such as age

From the Department of Cardiology, Thoraxcenter, University Hospital Rotterdam-Dijkzigt, Erasmus University, Rotterdam, The Netherlands.

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Address for reprints: Peter De Jaegere, MD, Department of Cardiology, Thoraxcenter, University Hospital Rotterdam-Dijkzigt, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

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Table 1. Total Number of Treated Patients With Subdivision According to the Administered Thrombolytic Agent and Occurrence of Intracranial Hemorrhage

Thrombolytic Agent	No. of Patients	ICH	%
Streptokinase	1,791	16	0.9
Alteplase (rt-PA)	283	2	0.7
Anistreplase (APSAC)	201	3	1.5
Saruplase/urokinase	194	3	1.5
Total	2,469	24	1*

*95% confidence interval 0.6% to 1.3%; chi-square test $p > 0.05$. APSAC = anisoylated plasminogen streptokinase activator complex; ICH = intracranial hemorrhage; rt-PA = recombinant tissue-type plasminogen activator.

and gender were noted as well as localization of the infarct, the choice of the thrombolytic agent, the time interval between the administration of thrombolytic therapy and the first clinical signs of an acute neurologic event, the diagnostic methods to evaluate the neurologic event and the clinical course and time interval between the first clinical signs of the event and subsequent death. A distinction was made between cardiac and neurologic death. Cardiac death was defined as death due to arrhythmia or heart failure, or both, in relation to myocardial infarction. Death due to intracranial hemorrhage was defined as the presence of clinical signs of loss of brain stem function (wide nonlight-reactive pupils, absence of cornea reflex and compensatory ocular movements and ultimately apnea).

For every case of intracranial hemorrhage and corresponding control cases, a case record form was completed by the first author at the participating center. The clinical characteristics were obtained from the medical records. In addition, reports by the paramedical staff and the results of computed tomography of the brain were reviewed.

Statistical methods. A chi-square test was used to assess the occurrence of intracranial hemorrhage in relation to the use of the various thrombolytic agents. The clinical characteristics were compared with use of Fisher's exact test. The difference in risk was expressed as the odds ratio with the corresponding 95% confidence interval. Univariate and multivariate logistic regression analyses were performed.

Results

Incidence. In a period of 18 months, 2,469 consecutive patients with acute myocardial infarction were treated with a thrombolytic agent in 61 hospitals. Twenty-four patients sustained intracranial hemorrhage, corresponding to an incidence rate of 1% (95% confidence interval 0.6% to 1.3%). Most patients were treated with streptokinase; however, the incidence of intracranial hemorrhage was equally distributed among patients receiving the various thrombolytic drugs (Table 1). The diagnosis of intracranial hemorrhage was confirmed by computed tomography of the brain in 18 patients and by necropsy in 1 patient. One patient had intraocular hemorrhage on fundoscopy and in four patients the diagnosis was based on clinical grounds without independent verification (Table 2). In all except three patients, the first clinical manifestations of acute hemorrhage were observed within 24 h after thrombolytic treatment (range 3 to 36 h, median 16). Sixteen patients (66%) died. All deaths among the patients with intracranial hemorrhage were classified as due to this bleeding complication. Thirteen patients died within 24 h after the diagnosis. The time interval between the diagnosis of intracranial bleeding and death ranged from 0.5 to 92 h (median 7.5).

Clinical predictive factors. Detailed data from 22 of the 24 patients were available. To augment the statistical power of the case control study, the data from nine other patients with documented intracranial hemorrhage (seven patients from the European Cooperative Study Group and two patients who sustained intracranial hemorrhage in our hospital outside the registry period) were added. In all, 31 patients were compared with 62 control patients. There was no statistical difference between the baseline characteristics of the 31 patients and the 62 control patients except for age (65 ± 8 in the study group vs. 59 ± 8 in the control group; $p < 0.02$) (Table 3). Body weight <70 kg was associated with a 3.4-fold higher risk of intracranial hemorrhage in association with thrombolytic therapy (Table 4). Among patients treated with streptokinase, the dose index (dose/body weight) was higher in patients with intracranial hemorrhage ($20,000 \pm 1,000$ U/kg) than in the control patients ($18,000 \pm 1,000$ U/kg; $p < 0.05$). Furthermore, age >65 years, hypertension at admission, the use of oral anticoagulant drugs before admission and the presence of diabetes were associated with a 2.3- to 4.4-fold higher probability of intracranial bleeding, although the confidence intervals crossed unity. The presence of peripheral vascular disease and history of hypertension did not appear to be associated with an increased risk, considering the wide confidence intervals. Because there was an equal distribution of the administration of intravenous and oral anticoagulant drugs and the use of antiplatelet therapy during the hospital stay between the patients with intracranial hemorrhage and the control patients, use of these drugs was not identified as a clinical risk factor for intracranial hemorrhage. The same was true for smoking.

Multivariate logistic regression analysis (Table 5) identified the use of anticoagulant drugs before admission, body weight <70 kg and age >65 years as independent clinical predictors for intracranial hemorrhage. These characteristics were associated with an increased risk of 5.7, 3.7 and 3.3, respectively.

Discussion

Incidence. Intracranial hemorrhage is the most dreaded complication of thrombolytic therapy, although the gain in survival in randomized trials exceeds the risk of intracranial hemorrhage. Pooled data from randomized comparisons of

Table 2. Clinical Signs and Localization of Intracranial Hemorrhage, Diagnostic Methods and Death in 33 Patients

Pt No.	Age (yr)/ Gender	Thrombolytic Agent	ASA	Heparin (IV)	Clinical Signs	Diagnostic Method	Hematoma Site	Fatal Outcome
Patients Recruited During Prospective Registry								
1	58/M	SK	−	−	Restless, coma, right hemiplegia	CT/necropsy	Right hemisphere	Yes
2	68/M	(Pro)-uro	−	+	Acute headache, right hemiplegia	CT	Left frontoparietal lobe	No
3	75/M	SK	+	+	Confused	CT	Right frontoparietal lobe	No
4	58/F	SK	+	+	Headache, nausea, vomitus, left hemiplegia	CT	Left temporal lobe	Yes
5	64/M	SK	−	+	Restless, right hemiplegia	CT	Left hemisphere	Yes
6	62/M	APSAC	−	−	Coma, quadriparalysis	Clinical	Fundo-oculi	Yes
7	62/M	APSAC	−	−	Confused	CT	Left temporal lobe	Yes
8	73/M	SK	−	+	Right hemiplegia	CT	Left frontoparietal lobe	Yes
9	65/M	SK	−	−	Left hemiplegia	CT	Right frontoparietal lobe	Yes
10	64/M	SK	−	+	Headache, confused, hemiplegia	Necropsy	Left occipital lobe	Yes
11	85/M	SK	+	+	Headache, confused	CT	Brain stem	No
12	60/F	SK	+	+	Headache, left hemiplegia	CT	Right frontoparietal lobe	No
13	71/F	rt-PA	+	+	Confused, right hemiplegia	CT	Left occipital lobe	No
14	60/M	SK	+	−	Headache, confused	CT	Right temporal lobe	No
15	70/F	(Pro)-uro	−	−	Restless	CT	Right frontal lobe	Yes
16	55/M	SK	+	+	Headache, right hemiplegia	CT	Left occipital lobe	Yes
17	61/M	SK	+	+	Coma	CT	Cerebellum	Yes
18	62/F	rt-PA	+	+	Confused	CT	Right parietal lobe	No
19	84/M	SK	+	+	Loss of consciousness	Clinical	?	Yes
20	50/M	SK	−	+	Headache, confused, right hemiplegia	Clinical	?	Yes
21	64/M	SK	+	+	Confused, coma	Clinical	?	Yes
22	70/M	(Pro)-uro	−	+	Acute loss of consciousness	Clinical	?	Yes
23	65/M	SK	−	+	Headache, paralysis left arm	CT	Nucleus caudatus, right thalamus	No
24	74/M	APSAC	+	+	Agitation, headache, coma	CT	Right temporal lobe	Yes
Patients Recruited Outside the Prospective Registry								
25	72/M	rt-PA	+	+	Confusion, coma	CT	Right frontoparietal lobe	Yes
26	74/M	SK	+	−	Headache	CT	Left parieto-occipital lobe, subarachnoidal and subdural regions	No
27	57/M	rt-PA	+	+	Hemiparesis	CT	Subdural region	No
28	57/M	rt-PA	+	+	Hemianopsia	CT	Occipital lobe	No
29	65/M	rt-PA	+	+	Left hemiplegia	CT	Right cortex	No
30	64/M	rt-PA	+	+	Diplopia, ataxia	CT	Cerebellum	No
31	67/M	rt-PA	+	+	Cerebellar syndrome	CT	Cerebellum and frontoparietal lobe	Yes
32	59/M	rt-PA	+	+	Confusion, headache	CT	?	No
33	64/M	rt-PA	+	+	Headache	CT	?	Yes

APSAC = anisoylated plasminogen streptokinase activator complex (30 U over 3 min); ASA = aspirin; CT = computed tomography of the brain; F = female; IV = intravenously; M = male; (Pro)-uro = (pro)-urokinase (100 mg over 60 min); Pt = patient; rt-PA = recombinant tissue-type plasminogen activator (100 mg over 6 h in all except Patient 13, who received 100 mg over 180 min, and Patient 18, who received duteplase (0.6 MU/kg over 4 h); SK = streptokinase (1.5 MU over 60 min in all patients except Patient 8, who received 3 MU); + = given; − = not given.

various regimens indicate incidence rates of intracranial hemorrhage expressed as the weighted average for each treatment group of 0.02% for placebo, 0.21% for streptokinase, 0.5% for alteplase and 0.21% for anistreplase (Table 6). The incidence rate of intracranial hemorrhage in the Second International Study of Infarct Survival (ISIS-2) (5) and in the International t-PA/SK mortality trial (13) was 0.1% and 0.3%, respectively, for streptokinase and 0.4% for alteplase. The higher incidence in this registry may be explained by the fact that, in common clinical practice, the inclusion and exclusion criteria for thrombolytic therapy are less stringent than those of prospective thrombolytic studies. Furthermore, differences in incidence reported in various studies may be related to the methods of patient selection and data

Table 3. Basic Characteristics and Treatment of Patients With Intracranial Hemorrhage and Control Patients

	Patients With Intracranial Hemorrhage	Control Patients
No.	31	62
Male	26 (84%)	48 (79%)
Age (yr)	65 ± 8	59 ± 8
Infarct		
Inferior	6 (19%)	11 (18%)
Inferoposterior	10 (32%)	28 (45%)
Anterior	10 (32%)	17 (27%)
Anterolateral	5 (16%)	3 (5%)
Lateral	0	3 (5%)
Treatment		
Streptokinase	15 (48%)	35 (57%)
Alteplase	10 (32%)	20 (33%)
(Pro)-urokinase	3 (10%)	6 (10%)
Anistreplase	3 (10%)	1 (2%)

collection, quality control and possibly as a result of the differences in thrombolytic agents, dosages and adjunctive therapy.

No difference was made between "primary" intracranial hemorrhage and hemorrhagic transformation of an ischemic stroke. Embolic cerebrovascular accidents occur in 0.7% to 0.9% of patients treated with placebo (5,8), 0.5% of patients treated with streptokinase (13) and 0.4% to 0.7% of patients treated with alteplase (8,14). Unfortunately, computed tomography of the brain is often of no help in making the differential diagnosis. Hemorrhagic conversion of cerebral infarction has been reported (14) to occur in about 30% of the patients with an ischemic cerebrovascular accident in association with acute myocardial infarction and thrombolytic therapy. Intracranial hemorrhage in association with thrombolytic therapy predominantly occurs within 24 h after initiation of treatment, whereas cerebral infarction supervenes after 48 h after the start of thrombolytic therapy (14). These factors illustrate the difficulty in defining the real incidence of this bleeding complication associated with administration of thrombolytic agents.

Table 4. Clinical Predictive Factors for Intracranial Hemorrhage by Univariate Analysis

	Odds Ratio	95% CI
Body weight <70 kg	3.4	1.3–9.0
History of diabetes	4.4	0.8–25.8
Anticoagulant drugs before admission	3.7	0.8–16.7
Hypertension at admission	2.6	0.8–8.2
Age >65 years	2.3	0.9–6.0
History of peripheral vascular disease	3.3	0.5–21.1
History of hypertension	1.2	0.5–3.3
Smoking	0.9	0.4–2.3
Heparin therapy during admission	0.8	0.3–2.6
Antiplatelet therapy during admission	0.7	0.2–1.7
Oral anticoagulant therapy during admission	0.6	0.2–1.9

CI = confidence interval.

Table 5. Clinical Predictive Factors for Intracranial Hemorrhage: Results of Multivariate Logistic Regression Analysis

	Odds Ratio	95% CI
Anticoagulant therapy before admission	5.7	1.1–29.4
Body weight <70 kg	3.7	1.4–9.8
Age >65 years	3.3	1.2–10.0

CI = confidence interval.

No difference in incidence of intracranial hemorrhage was noted among patients receiving the various thrombolytic drugs. However, the number of patients who sustained intracranial bleeding in our study precludes a definitive conclusion (Table 1). In the International t-PA/SK mortality trial (13), including >10,000 patients randomized to either alteplase or streptokinase, 43 patients (0.42%) treated with alteplase and 30 patients (0.29%) in the streptokinase group sustained intracranial bleeding. This corresponds to an excess risk of 0.13% with alteplase, with a 95% confidence interval ranging from −0.04% to 0.29%. Moreover, there was an equal number of ischemic strokes in both groups, but a higher number of patients with an unclassified stroke in the alteplase group, of whom a number patients will have sustained cerebral hemorrhage. The preliminary results of the Third International Study of Infarct Survival (ISIS-3) (32), in which >40,000 patients were randomized to either streptokinase, anistreplase or duteplase, the latter being a double-chain tissue plasminogen activator (t-PA) with a different molecular structure from that of the predominantly single-chain alteplase, seems to confirm the higher rate of intracranial hemorrhage after recombinant tissue-type plasminogen activator (rt-PA) administration.

Clinical predictive factors. To determine clinical predictive factors for intracranial hemorrhage, a case-control study was conducted. Such a study design has been shown to be the most efficient and reliable method to study rare events (15,16). Multivariate logistic regression analysis identified anticoagulant therapy before admission, low body weight and age >65 years as independent predictive risk factors for intracranial hemorrhage. Oral anticoagulant drugs are known to be associated with an increased risk of "spontaneous" intracerebral hemorrhage and other bleeding complications (33). Apparently this risk is enhanced in association with thrombolytic therapy.

Intracranial hemorrhage occurred more frequently in patients with a low body weight. Because the dose index of streptokinase was higher in patients with intracranial hemorrhage than in the control patients ($p \leq 0.05$), this is most likely explained by an "overdosing" of the patients who sustained intracranial hemorrhage. If these findings are confirmed by other trials, the dose of streptokinase should be adjusted for body weight. A difference in the dose index of recombinant t-PA (rt-PA) was not found in this study. However, a dose-related risk of intracranial hemorrhage had

Table 6. Frequency of Intracranial Hemorrhage in Association With Thrombolytic Therapy Expressed as Weighted Average of Pooled Data From Randomized Trials

Treatment	No.	ICH	%	95% CI	Reference
Placebo	13,141	2	0.02	0.00–0.06	2,3,5–8,17–23
Streptokinase	20,652	43	0.21	0.15–0.27	2,3,5,6,10,11,13,24–28
Alteplase	17,894	88	0.5	0.41–0.59	7,8,10,11,13,17–19,24,25,29–31
Anistreplase	1,940	4	0.21	0.01–0.41	20–23,26–28

Abbreviations as in Tables 1 and 4.

been reported for alteplase and was the reason that the dose of alteplase was reduced from 150 to 100 mg/6 h in the Thrombolysis in Myocardial Infarction (TIMI) Trial (34).

Patients >65 years old had a threefold higher probability of cerebral hemorrhage. This finding is in agreement with the findings of the TIMI-II Trial (14) and is probably related to more common defects in cerebrovascular integrity. Congophylic amyloid angiopathy is prevalent in the elderly (35,36). Fibrinolysis may disrupt the naturally occurring microhemostasis in cerebral vessels and thus induce bleeding. Moreover, previous studies (37,38) reported age to be an independent risk factor for other bleeding complications after thrombolytic therapy.

Traditional teaching is that chronic high blood pressure is a cause of cerebral hemorrhage, but a recent review (33) has questioned this hypothesis, our results did not indicate such a relation unequivocally; however, hypertension at admission seemed to be associated with an increased bleeding risk, although the relation was not statistically significant (Table 4).

Heparin therapy by itself has a low likelihood of causing cerebral bleeding. The use of heparin for treatment of ischemic stroke is associated with a 0.8% incidence rate of hemorrhagic stroke (39). The contribution of heparin therapy to the occurrence of intracranial hemorrhage in association with thrombolytic therapy is not fully understood (40). In this study, heparin was not identified as a risk factor. Similarly, antiplatelet therapy with aspirin appeared not to be associated with an increased risk for intracerebral bleeding (5).

Conclusions. Intracranial hemorrhage in association with thrombolytic therapy occurs in 1% of the patients. Patients using oral anticoagulant drugs before admission and those with a low body weight and age >65 years seem to be at higher risk. However, the confidence intervals were wide and the true impact of these risk factors is not known. It is very possible that other or larger studies will reveal additional risk factors for intracranial hemorrhage. The current analysis indicates that thrombolytic therapy should not be administered to those patients with an increased risk for intracranial hemorrhage in whom a limited benefit of thrombolysis may be suspected. This group would include, for example, elderly patients who develop a small inferior myocardial infarction despite ongoing therapy with anticoagulant drugs. If more extensive data become available, a risk-benefit analysis of therapy would be feasible in each patient before initiation of thrombolytic therapy.

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